RESEARCH ARTICLE

Maternal Stress during Pregnancy, ADHD Symptomatology in Children and Genotype: Gene-Environment Interaction

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Abstract

Objective: Case control studies suggest a relationship between maternal stress during pregnancy and childhood ADHD. However, maternal smoking, parenting style and parental psychiatric disorder are possible confounding factors. Our objective was to control for these factors by using an intra-familial design, and investigate gene-environment interactions. **Methods:** One hundred forty two children, ages 6 to 12, (71 with ADHD, and their 71 non-ADHD siblings) participated in the intra-familial study design. A larger sample of ADHD children (N=305) was genotyped for DAT1 and DRD4 to examine gene-environment interactions. Symptom severity was evaluated using the Child Behavior Checklist (CBCL) and the Conners' Global Index for Parents (CGI-P). The Kinney Medical and Gynecological Questionnaire was used to report stressful events during pregnancies. **Results:** Logistic regression indicated that mothers were more likely to have experienced high stress during pregnancy of their ADHD child compared to that of the unaffected sibling (OR: 6.3, *p*=.01). In the larger sample, DRD4 7/7 genotype was associated with increased symptom severity in the high stress pregnancy (*p*=.01). **Conclusions:** Maternal stress during pregnancy was associated with the development of ADHD symptomatology after controlling for family history of ADHD and other environmental factors. This association could partly be mediated through the DRD4 genotype.

Key words: *ADHD, prenatal stress, pregnancy, DRD4*

Résumé

Objectifs: Les études de cas-témoins laissent croire qu'il existe une relation entre le stress maternel pendant la grossesse et le TDAH chez les enfants. Cependant, le tabagisme maternel, le style parental et les troubles psychiatriques chez les parents sont des facteurs confondants possibles. L'objectif de notre étude était de contrôler ces facteurs en utilisant une approche intrafamiliale et d'investiguer les interactions entre les gènes et l'environnement. **Méthodologie:** Cent quarante-deux enfants âgés de 6 à 12 ans (71 souffrant de TDAH et 71 frères ou sœurs sans TDAH) ont participé à une étude intrafamiliale. Les gènes DAT1 et DRD4 ont été étudiés dans un échantillon plus large d'enfants souffrant de TDAH (N=305) afin d'analyser les interactions gènes-environnement. La gravité des symptômes a été évaluée en se basant sur le Child Behavior Checklist (CBCL) (Liste de vérification du comportement), et sur le Conners' Global Index for Parents (CGI-P) (Échelle globale d'évaluation Conners – version du parent). Le Kinney Medical and Gynecological Questionnaire a servi à consigner les événements stressants pendant la grossesse. **Résultats:** La régression logistique a indiqué qu'il est plus probable que les mères aient subi de hauts niveaux de stress durant la grossesse de leur enfant avec TDAH par rapport à celle de leur frère ou de leur sœur. (OR : 6.3, p=.01). Dans l'échantillon élargi, le génotype DRD4 7/7 a été associé à des symptômes plus graves dans le groupe des mères qui avaient subi un haut niveau de stress durant leur grossesse (p=.01). **Conclusions:** Après avoir vérifié les antécédents familiaux de TDAH et certains facteurs environnementaux, nous constatons qu'il existe une relation entre le stress maternel pendant la grossesse et l'apparition des symptômes de TDAH. Cette relation s'exprime en partie à travers le génotype DRD4.

Mots clés: *TDAH, stress prénatal, grossesse, DRD4*

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is among the most commonly diagnosed behavioral disorders in children, with prevalence estimates in North America ranging from 6%-12%. It is clinically characterized by hyperactivity, impulsivity and inattention. These symptoms often continue into adulthood and may lead to an increase of family conflict, poor occupational performance and academic failures throughout adult life (Biederman & Faraone, 2005).

The etiology of ADHD is complex and multifactorial. While twin and adoption studies indicate that genetic factors are critical determinants of ADHD, with a heritability estimate of 76% (Faraone et al., 2005), environmental factors are also thought to contribute to the emergence and severity of the disease. Many of these factors seem to cluster around pregnancy and birth, including obstetrical complications, maternal smoking, alcohol use and stress during pregnancy (Grizenko, Shayan, Polotskaia, Ter-Stepanian, & Joober, 2008; Linnet et al., 2003). Other environmental contributing factors include parental mood disorders, psychosocial adversity and parenting style (Langley, Holmans, van den Bree, & Thapar, 2007).

Prenatal stress has been associated with negative outcomes in children from infancy to school age. Epidemiological studies have shown that prenatal stress increases the rate of spontaneous abortions, fetal malformations, and preterm birth (Hedegaard et al., 1996). Toddlers born to stressed mothers have worse general intellectual and language functioning (Laplante et al., 2004). In a large-scale community, O'Connor et al. (O'Connor, Heron, Golding, & Glover, 2003) found a robust link between prenatal stress and externalizing problems in children at four and six years.

Activity of the hypothalamic-pituitary-adrenal (HPA) axis is thought to play a key role in mediating the effects of maternal stress on the fetus. Activation of the HPA axis, in response to physical or psychological stress, results in the release of circulating cortisol. In highly stressful situations, elevated maternal cortisol could exceed the placental capacity to degrade it, cross the placental barrier and influence the developing brain and/or 'program' the fetal HPA axis (Seckl & Holmes, 2007). Alternatively, maternal stress could cause a constriction of the uterine artery, leading to decreased blood flow to the fetus. The resulting fetal hypoxia may hinder fetal development and predispose the child to problems later in life (Teixeira, Fisk, & Glover, 1999).

The aim of this study was twofold; first, to examine the relationship between maternal exposure to stress and ADHD in children. Second, to explore possible gene-environment interactions (GxE) involving prenatal stress in ADHD children. Previous studies found an association between prenatal stress and ADHD (Grizenko et al., 2008; Li, Olsen, Vestergaard, & Obel, 2010; van den Bergh & Marcoen, 2004); however, the majority did not systematically control for confounding factors such as parenting style, home environment, parental mood disorders or parental ADHD. In the present study, all of these factors were controlled for by using an intra-familial control group consisting of siblings of the ADHD probands. This study investigates whether mothers experienced a greater level of stress during the pregnancy of their ADHD child compared to their unaffected sibling.

Given the potential role of prenatal stress in the development of childhood psychopathology, we were interested in investigating whether this factor may interact with candidate genes to produce greater symptom severity. We selected candidate genes which are implicated in neurotransmission in ADHD and where associations have been supported in meta-analyses. The dopaminergic system has long been implicated in the pathogenesis of ADHD. One of the most replicated molecular genetic findings is an association between ADHD and the 7-repeat allele of a 48 base-pair variable number tandem repeat (VNTR) of the dopamine receptor 4 (DRD4) gene (Li, Sham, Owen, & He, 2006). Studies of the human dopamine transporter (DAT1) gene have revealed a possible association between alleles of the VNTR located in the 3' untranslated region (3'-UTR) of DAT1 and ADHD (Gizer, Ficks, & Waldman, 2009). In this paper, we explored GxE interactions implicated in the pathogenesis of ADHD by investigating whether maternal stress during pregnancy interacts with these genotypes to produce more severe symptomatology.

Several potential candidate GxE interactions in childhood ADHD have recently been investigated. These studies have demonstrated a diathesis-stress relationship, whereby a genetic vulnerability coupled with an environmental stress will increase the likelihood of a disordered behavior. Certain haplotypes of DAT1 have been shown to interact in diverse ways with maternal smoking during pregnancy (Neuman et al., 2007), prenatal alcohol exposure (Brookes et al., 2006) and psychosocial adversity (Laucht et al., 2000) to produce different severity of these phenotypes. Significant GxE interactions have also been found between DRD4 and maternal smoking (Neuman et al., 2007). To date, no other study has examined the relationship between maternal stress during pregnancy and child genotype in the pathogenesis or severity of ADHD.

Methods

Sample

Subjects were recruited from the Disruptive Behavior Disorders Program and the children's outpatient clinics of the Douglas Mental Health University Institute (DMHUI), a

psychiatric teaching hospital in Montreal, Canada. They were referred to the clinic by schools, social workers, family doctors and pediatricians. This study was approved by the Research and Ethics Board of the DMHUI. Ninety-five percent of eligible subjects agreed to participate. All participating children agreed to take part in the study, and parents signed informed consent forms. Probands were diagnosed with ADHD by an experienced child psychiatrist according to DSM-IV criteria, based on a clinical evaluation with the family, observation of the child, school reports and an interview with parents using the Diagnostic Interview Schedule for Children Version IV (DISC-IV) (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). Exclusion criteria included an IQ of less than 70, as assessed by the Wechsler Intelligence Scale for Children III (WISC-III), or a history of Tourette's syndrome, psychosis or pervasive developmental disorder.

Assessment

Parents were interviewed regarding the ADHD history of all their children. Siblings who did not have ADHD were identified based on the DISC-IV, and the child closest in age and of the same sex as the proband, if possible, was included in the study. Both probands and siblings were also assessed using the Child Behavior Checklist (CBCL) and the Conners' Global Index for Parents (CGI-P) (Achenbach, 1991; Conners, 2003).

Obstetric complications were assessed using the Kinney Medical and Gynecological Questionnaire and scored using the McNeil-Sjöström scale (McNeil, Cantor-Graae, & Sjostrom, 1994). During this interview, mothers were asked to describe stressful life events experienced during their pregnancy with each child, and this information was used to score maternal stress levels from 1 to 5 based on the DSM-III and DSM-III-R axis IV scales (1 = no stress, 2 = mild, 3 = moderate, 4 = severe and 5 = extreme). To corroborate these results and decrease recall bias, we examined medical and obstetrical records and separately interviewed another person close to the mother, such as her husband or her own mother, who were present during the pregnancies. Subjects were divided into two categories: those whose mother had experienced no or mild stress during pregnancy (such as arguments with friends) and those whose mother had experienced moderate, severe or extreme stress during pregnancy. Examples of moderate-to-extreme stress include separation, repeated physical or sexual abuse, imprisonment of a spouse or death of a very close relative during pregnancy. All moderate/extreme stressors reported by the mothers were corroborated with a separate interview with a close family member.

Genotyping

Genotypes were determined using a blood or saliva sample. PCR amplification of the DRD4 exon 3, 48 bp-VNTR and DAT1 3'-UTR VNTR was performed according to Lichter et al. (1993) and Vandenbergh et al. (1992) respectively.

Data analysis

To examine the relationship between ADHD diagnosis and maternal stress, we used a sub-sample of matched subject pairs consisting of the ADHD probands and their non-ADHD siblings (71 pairs). Paired t-tests were used to compare the demographic and clinical characteristics of the two groups. Next, a conditional logistic regression for matched pairs was conducted, into which we modeled the effects of maternal stress, gender and age.

To test for GxE interactions, we needed a large number of subjects, so we used all subjects that have participated in the study so far (N=305), which included the 71 ADHD kids who have an unaffected sibling, but also those who do not have any sibling, and those whose sibling also had ADHD. The siblings themselves were not included in the genetic analysis, as they are not independent from the probands. As is often the case with the DRD4 and DAT1 genes, only the most frequent alleles were entered in the analysis (DRD4: 4 and 7 repeat alleles; DAT1: 9 and 10 repeat alleles). Two-way ANOVA was used to evaluate the interaction between prenatal stress and genotype in the severity of ADHD symptoms, as measured by the CBCL and CGI-P scores. Post-hoc Tukey's Honestly Significant Difference tests were performed when appropriate.

Results

Demographic and clinical characteristics of the sample

Table 1 shows the demographic characteristics of ADHD and non-ADHD children in the sample. In the paired sibling sub-sample, ADHD children were significantly younger than their unaffected siblings ($p < 0.01$). The proportion of boys was significantly higher in the proband group (89% male, 11% female) than in the sibling control group (51% male, 49% female), reflecting the fact that boys are more frequently diagnosed with ADHD than girls. There was no significant difference in family income, mother's age at child's birth, postnatal stress levels, obstetrical complications and maternal smoking and alcohol consumption during pregnancy between the two groups. In the large sample consisting of all probands, ethnic origin of the subjects was as follows: 85.2% white, 5.8% half-white, 4.3% black, 2.0% aboriginal and 2.6% other (Persian, Arabic and Asian). Genotype frequencies were in Hardy-Weinberg

Table 1. Demographic characteristics of ADHD and non-ADHD children in our sample

	All probands (GxE study) n = 305	Paired siblings sub-sample			
		ADHD n = 71	Non-ADHD n = 71	*t* or χ^2	*p* value
Gender, M/F	248/57	63/8	36/35	24.3	<.01
Age, yr (SD)	8.9 (1.8)	9.0 (1.8)	9.9 (2.5)	2.6	.01
Income group[a] (SD)	4.3 (1.6)	4.4 (1.5)	4.5 (1.5)	0.4	.70
Maternal smoking during pregnancy, yes/no	147/156	27/44	27/44	0.0	1.0
Maternal alcohol consumption during pregnancy, yes/no	80/221	17/54	16/55	0.4	.84
Obstetric complications[b], yes/no	247/51	55/16	61/10	1.7	.28
Stress during pregnancy, high/low	161/144	29/42	14/57	7.5	.01
Postnatal stress, high/low	60/238	5/66	4/67	0.1	.73
Mother's age at child's birth, y (SD)	27.4 (5.6)	28.1 (5.9)	28.0 (6.1)	0.9	.40

Abbreviations: GxE: gene x environment interaction; SD: standard deviation; M: male; F: female; yr: years of age

[a] Income was grouped into 6 categories: (1) < CAN$6,000 (2) CAN$6,000 - $10,000 (3) CAN$10,000 - $20,000 (4) CAN$20,000 - $30,000 (5) CAN$30,000 - $40,000 (6) CAN > $40,000

[b] Presence of obstetric complication defined as a rating of 4 or above on the McNeil-Sjöström scale.

Table 2. Logistic regression analysis of ADHD subjects and their non-ADHD sibling

	B	SE	p value	OR	95% CI
Child's gender	2.79	0.81	<0.01	16.35	3.34-79.15
Child's age	-0.20	0.13	0.13	0.82	0.63-1.06
Maternal stress during pregnancy	1.84	0.75	0.01	6.29	1.45-27.26

Abbreviations: B: unstandardized regression coefficient; SE: Standard Error; OR: Odds Ratio; CI: Confidence Interval

equilibrium, and did not significantly differ between the ADHD and non-ADHD siblings.

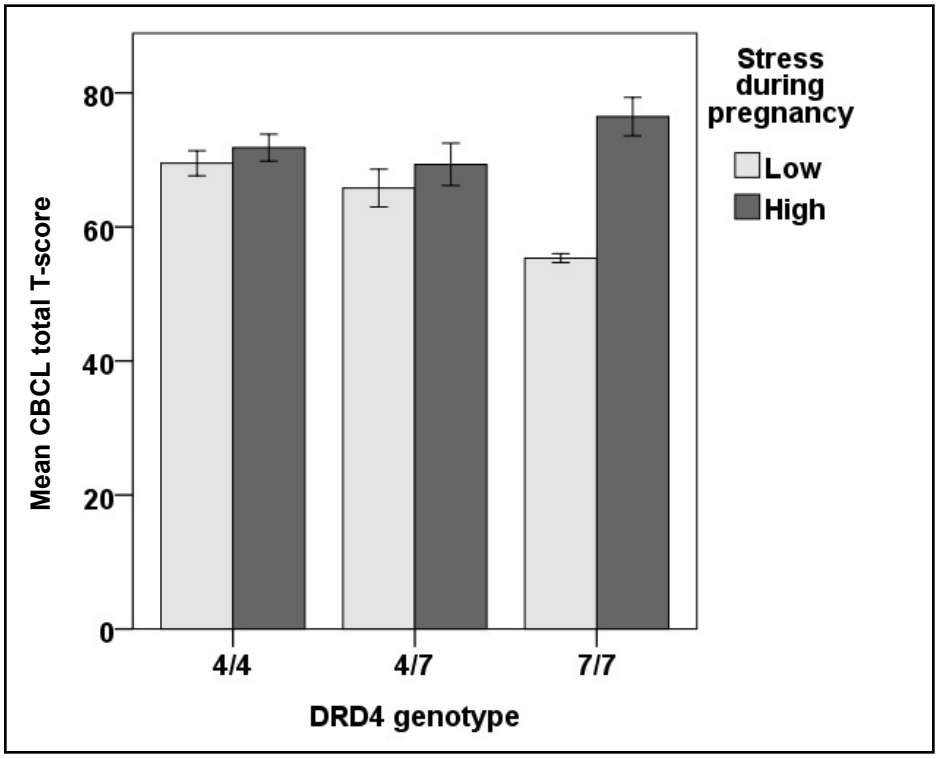
Prenatal stress and ADHD diagnostic

ADHD children scored significantly higher than their unaffected siblings on the CBCL (74.3±9.5 [SD] and 50.1±10.1; $p<.01$) and CGI-P (69.7±8.4 and 50.6 ± 12.8, respectively; $p<.01$). A conditional regression model was fitted to the case-control data to evaluate the effects of maternal stress on ADHD diagnostic. Sex and age were also included in the model. Regression analysis revealed a significant effect of maternal stress during pregnancy (Table 2; odds ratio [OR]=6.29, $p=.01$) and child's gender (OR=16.35, $p<.01$), but no significant effect of age (OR=0.82, $p=.13$).

Gene X Environment Interactions

For the DRD4 gene, genotype frequencies were as follows: 4/4=123, 4/7=74, 7/7=14, others=75. Two-way ANOVA revealed a significant interaction between DRD4 genotype and maternal stress on the total CBCL T-score (Figure 1; $F_{2,200}=5.99$, $p<.01$), a significant effect of maternal stress ($F_{1,200}=22.09$, $p<.01$) and of genotype ($F_{2,200}=4.25$, $p=.02$). The effects of maternal stress were globally to increase symptom severity. However, the effects were more pronounced in 7/7 individuals who, in the absence of maternal stress, displayed the lowest average T-score (55.33±0.6) and in the presence of stress, displayed the highest (76.45±4.8). In addition, post-hoc analysis revealed that 4/4 individuals had a significantly higher symptom score compared to 4/7 individuals. There was no significant interaction between stress and DRD4 on the CGI-P ($F_{2,187}=1.87$, $p=.16$), but a significant effect of genotype ($F_{2,187}=5.50$, $p<.01$) and maternal stress (F1,187=8.43, $p<.01$) was observed. Post-hoc tests indicated again that subjects with the 4/4 genotype displayed more severe symptoms than those with the 4/7 genotype. DAT1 genotype frequencies were as follows: 9/9=23; 9/10=119; 10/10=145; others=18. Two-way ANOVA indicated no significant interaction between the effects of DAT1 genotype and maternal stress and no effect of genotype alone on CBCL or CGI-P scores. However, we observed a significant effect of maternal stress on both symptom scales (CBCL: $F_{1,276}=8.55$, $p<.01$; CGI-P: $F_{1,256}=11.17$, $p<.01$). In all GxE investigated, maternal stress systematically increased symptom severity, lending further

Figure 1. Symptom severity in children as measured by the CBCL, presented according to the level of prenatal stress and DRD4 genotype. Data analysis showed a significant GxE interaction (p=.01), with children homozygous for the 7-repeat allele being particularly sensitive to high prenatal stress exposure compared to low stress exposure.



support to the key role of prenatal maternal stress in childhood psychopathology.

Discussion

The main finding of this study is that children with ADHD have been exposed to higher levels of maternal stress during pregnancy (OR = 6.3), compared to their unaffected siblings. This result validates many previous reports and controls largely for potential family environment and genetic confounders. Prenatal stress may have a lasting impact on the child's behaviour (Grizenko et al., 2008; Rodriguez & Bohlin, 2005; van den Bergh & Marcoen, 2004). However, these studies did not take into account other environmental risk factors that often co-occur with maternal stress such as parenting style, parental psychiatric disorders, and home environment. By using unaffected siblings as a control group, we were able to control, to a certain extent, for these factors and for genetic background. Furthermore, it is crucial that any study examining the relationship between maternal stress and childhood ADHD also takes into account maternal smoking during pregnancy, one of the most frequently reported environmental risk factors for ADHD (Langley et al., 2007). In this study, the sibling control group allowed us to control for this factor. In fact, every single mother in our sample had consistent smoking behavior throughout both pregnancies studied. Similarly, alcohol consumption during pregnancy did not predict a diagnosis of childhood ADHD in our study, as maternal alcohol consumption was consistent across pregnancies in all but one mother.

Furthermore, in our study, the DRD4 7/7 genotype was associated with more severe psychopathology, as shown by the higher CBCL and CGI-Parents scores. This finding is in line with many studies and meta-analyses that observed an association between ADHD and the 7-repeat allele (Gizer et al., 2009; Li et al., 2006). We also observed significantly elevated symptom severity in 4/4 compared to 4/7 carriers. Most of the literature hints at a protective effect of the 4-repeat allele (Li et al., 2006); however, here we report an effect on symptom severity, not an association with ADHD risk per se, as all probands have an ADHD diagnosis. It is possible that the 4-repeat allele does not increase ADHD risk by itself but increases the severity of the illness in the presence of other genetic/environmental factors.

Lastly, our study suggests that maternal stress during pregnancy may interact with the child's DRD4 7/7 genotype to produce more severe ADHD symptoms, as measured by the CBCL total T-score and the CGI-P. Similarly, Neuman et al. (2007) observed that the risk for a diagnosis of ADHD was significantly elevated in twins with prenatal smoke

exposure and the DRD4 7-repeat allele. Taken together, these results suggest that the 7-repeat allele might be implicated in both the development and severity of ADHD. Given our limited sample size, however, these results need to be replicated in a larger sample with more genetic variability to confirm their validity. It is worth noting that this interaction was identified in the presence of main effects for maternal stress during pregnancy as well as genotype.

Limitations

Prospective studies are generally considered an ideal design to evaluate effects of risk factors on traits present in the general population. However, when the trait under study (e.g. ADHD) is present only in a fraction of the population, the cost of recruiting and following a sample large enough to contain a significant number of affected individuals constitutes a serious drawback. For instance, in a prospective study by Rodriguez and Bohlin (2005), only 7 participants out of the 208 (i.e. 3.4%) who entered the study actually developed ADHD. Furthermore, to show an interaction between a less frequent genotype such as the 7/7 DRD4 alleles and maternal stress, one needs a large sample of individuals with the disorder. Thus, a group-control study appears to be the best alternative.

Nevertheless, the fact that this is a retrospective study poses some limitations, particularly our reliance on maternal recall to evaluate maternal stress during pregnancy which may be skewed by the child's ADHD diagnosis. Several strategies were implemented to minimize these effects. First, results of the Kinney Medical and Gynecological Questionnaire were corroborated with medical and hospital obstetrical records. We also separately interviewed another person close to the mother (e.g. her husband or her own mother) to confirm her account of stressful events (both in probands and their unaffected siblings). Finally, to minimize the effects of subjectivity and recall bias, mothers were divided into two groups: those who had experienced no or mild stress during pregnancy versus moderate to severe stress. Stressors in the latter group were major life events that were easily placed in time and their stress effects were not in dispute, such as a divorce, death of a first degree relative, incarceration of a spouse, or loss of a home due to fire.

Much of the strength of this study lies in its use of an intrafamilial control group to control for environmental and to a certain extent, genetic factors. Rarely, siblings did not share two parents (i.e. half-siblings, n=7), which would lessen the genetic similarity between them. Siblings of probands who were themselves affected by ADHD were not included in this sample, which was often the case for the male siblings of ADHD children. This explains why the unaffected siblings control group contains more girls than boys.

Finally, investigations of GxE interactions suffer from some limitations that must be kept in mind when interpreting the results. Some variables, such as maternal susceptibility or resilience to stress, may be partly under genetic influence. In such a case, the GxE interaction observed might in fact constitute a gene-environment correlation, or even a gene-gene interaction.

Conclusion

Our study shows that maternal stress during pregnancy increases the risk of ADHD diagnosis later in life, independently of other factors that have been previously reported. Furthermore, our results suggest that this relationship may partially be mediated through the DRD4 7/7 genotype. The study illustrates the need for increased support to pregnant women whose children are at higher risk of developing ADHD symptoms, and the potential use of genotyping in predicting this risk.

Acknowledgements / Conflicts of Interest

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